CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-532

ADMINISTRATIVE DOCUMENTS

13. PATENT INFORMATION

Relevant method of use, pharmaceutical composition, and active pharmaceutical ingredient (chemical entity) patent information for Benicar HCT™ Tablets is provided on the following page.

PATENT INFORMATION

U.S. Patent Number: 5,616,599

Date of Expiration: April 1, 2014

Type of Patent: Active Pharmaceutical Ingredient, Pharmaceutical Composition and Method of Use Patent

Patent Owner: Sankyo Company, Limited
Tokyo, Japan

Original Declaration:

The undersigned declares that U.S. Patent No. 5,616,599 covers the Active Pharmaceutical Ingredient (chemical entity), Pharmaceutical Composition and Method of Use of the olmesartan medoxomil component of Benicar HCT™, which is an oral antihypertensive agent. This product is the subject of this application for which approval is being sought.

SANKYO PHARMA INC.

By: _____ Date: June 20, 2002

Richard S. Barth, Esq.
Frishauf, Holtz, Goodman & Chick, P.C.
767 Third Avenue
New York, NY 10017-2023

EXCLUSIVITY SUMMARY FOR NDA # 21-532 SUPPL #_____

Trade Name: Benicar HCT Generic Name: olmesartan medoxomil/hydrochlorothiazide Tablets

Applicant Name: Sankyo Pharma Inc. HFD # 110

Approval Date If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X__/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /_ __/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?
3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X__/ NO /_ __/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-286 olmesartan medoxomil

NDA# 11-835 hydrochlorothiazide

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data,

would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study #: CS-866-318

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the

effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doug Throckmorton
4/17/03 12:10:17 PM

16. DEBARMENT CERTIFICATION

July 9, 2002

CERTIFICATION PURSUANT TO 21 U.S.C. 306(K)(1)

Sankyo Pharma Inc. hereby certifies that it did not use and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

By: Thomas D. Robinson, M.D.

Thomas Robinson, M.D.
Vice President, Clinical Development
Sankyo Pharma Development

4 Page(s) Withheld

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-532	New Combination-4S Indication-Hypertension	
Drug: Benicar HCT (olmesartan medoxomil/HCTZ), 20/12.5, 40/12.5, and 40/25 mg.	Applicant: Sankyo Pharma Co.	
RPM: E. Fromm	HFD-110	Phone # 594-5332
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	4S
• Other (e.g., orphan, OTC)	
❖ User Fee Goal Dates	June 5, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerat approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	PM-June 3, 2003
[redacted]	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	Not applicable
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	NA
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	ODS (Tradename-October 25, 2002 & April 15, 2003)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	X
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	NA
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	NA
• Pre-NDA meeting (indicate date)	NA
• Pre-Approval Safety Conference (indicate date; approvals only)	NA
• Other (Development)	February 16, 2000

❖ Advisory Committee Meeting	
• Date of Meeting	NA
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	NA
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Div. Director-May 27, 2003 Sec. Medical Review-May 7, 2003
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	Safety-February 28, 2003 Efficacy-April 10, 2003
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	NA
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	Included in Dr. Gordon's review of February 28, 2003
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	NA
❖ Statistical review(s) *(indicate date for each review)*	March 1, 2003
❖ Biopharmaceutical review(s) *(indicate date for each review)*	April 10, 2003
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Not Requested
• Bioequivalence studies	NA
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	Yes-April 4, 2003
• Review & FONSI *(indicate date of review)*	NA
• Review & Environmental Impact Statement *(indicate date of each review)*	NA
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	NA
❖ Facilities inspection (provide EER report)	Date completed: January 9, 2003 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (x) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	March 27, 2003
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	NA
❖ CAC/ECAC report	NA

RHPM NDA Overview
June 3, 2003

NDA 21-532 Benicar HCT (olmesartan medoxomil/hydrochlorothiazide) 20/12.5, 40/12.5, and 40/25 mg Tablets

Sponsor: Sankyo Pharma

Classification: 4S

Indication: Treatment of Hypertension

Date of Application: August 5, 2002
Date of Receipt: August 5, 2002
10-Month Goal Date: June 5, 2003

Background

Sankyo has submitted this NDA for the combination product olmesartan medoxomil/HCTZ for the treatment of hypertension. Olmesartan monotherapy was approved for the treatment of hypertension under NDA 21-286 on April 25, 2002. Studies for the combination for the treatment of hypertension were performed under IND The pivotal trial supporting this application was CS-866-318, "A Randomized, Placebo-Controlled, Factorial-Design Study of CS-866 and Hydrochlorothiazide in Patients with Essential Hypertension".

Meetings

September 11, 2002	Filing Meeting
February 16, 2000	Clinical Guidance

Review

Medical

Division Director:	Douglas C. Throckmorton, M.D
Conclusion:	Approval, subject to agreement on labeling (see Dr. Throckmorton's May 28, 2003 Division Director's Memo).
Seconday Medical:	Abraham Karkowsky, M.D., Ph.D.
Conclusion:	Dr. Karkowsky states in his May 7, 2003 review that "the proposed strengths of olmesartan/hydrochlorothiazide: 21/12.5, 40/12.5 and 40/25 mg should be approved", he notes further that a dosing strength of would be helpful in titrating the drug but this strength would require a bioequivalence study and additional stability data.
Labeling:	Dr. Karkowsky recommended changes to the **CLINICAL PHARMACOLOGY, PRECAUTIONS,** and **DOSAGE AND ADMINISTRATION** sections of the labeling (see reviewer's internal mark-up of the sponsor's labeling).
Medical Reviewers:	Maryann Gordon, M.D. (Safety)

Conclusion: Salma Lemtouni, M.D., M.P.H., (Efficacy)
(Safety)-Dr. Gordon, in her February 28, 2003 review, said that only the adverse event of dizziness appears to be linked to the use of the combination product (study 866-318). It appears that there are no major safety issues from her review.
(Efficacy)-Dr. Lemtouni, in her May 8, 2003 review, said that the 40/25 combination dose is approvable for the treatment of hypertension in patients with no concomitant diseases including hypertension end-organ damage. She also noted that the strengths of [redacted] would be helpful in dosing patients, provided that bioavailability studies could support such strengths.

Labeling: Dr. Lemtouni recommended changes to the **CLINICAL PHARMACOLOGY** section of the labeling (see reviewer's internal mark-up of the sponsor's labeling).

Statistical
Statistical Reviewer: James Hung, Ph.D.
Conclusion: Dr. Hung stated in his January 31, 2003 review that "all six non-zero dose combinations (i.e., CS-866 [redacted] CS-866 20 mg/HCTZ 12.5 mg, CS-866 20 mg/HCTZ 25 mg, CS-866 40 mg/HCTZ 12.5 mg, CS-866 40 mg/HCTZ 25 mg) are more effective than placebo (p-value <0.0001 for each) on sitting DBP reduction."

Labeling: None

Biopharmaceutics
Reviewer: Nhi Nguyen, Pharm.D.
Conclusion: Approvable, a biowaiver is granted for the 40/25 mg tablet.
Labeling: Dr. Nguyen did not suggest any labeling changes, but asked that the following dissolution specifications be listed in the approvable/approval letter:

CS-866 (olmesartan medoxomil)

Medium:	900 ml, JP fluid 2, pH 6.8, 37°C
Apparatus:	USP II (paddle)
Speed:	50 rpm
Specifications:	Q not less than [redacted] at 45 minutes

HCTZ

Medium:	900 ml, JP fluid 2, pH 6.8, 37°C
Apparatus:	USP II (paddle)
Speed:	50 rpm
Specifications:	Q not less than [redacted] at 15 minutes

Chemistry
Reviewer: Monica Cooper, Ph.D.
Conclusion: Dr. Cooper, in her April 23, 2003 review, stated that drug is recommended for approval from a chemistry, manufacturing and controls standpoint.

Labeling: Dr. Cooper suggested changes to the **DESCRIPTION** and **HOW SUPPLIED** sections of the labeling. She also asked that the statement "Based on the provided stability data, the expiration date for Benicar HCT tablets packaged in [redacted] bottles and [redacted] blisters is 18 months, when stored at 20-25°C."

CGMP Inspections: Acceptable, January 9, 2003

Methods Validation: Pending

Environmental Assessment: Exclusion granted

Pharmacology

Reviewer: Gowra Jagadeesh, Ph.D.

Conclusion: Approvable

Labeling: In his March 27, 2003 review, Dr. Jagadeesh suggested changes to the **WARNINGS, Fetal/Neonatal Morbidity and Mortality** subsection of the labeling.

Safety Update: Included in Dr. Gordon's February 28, 2003 medical review (see pg. 31).

Patent info: acceptable

DSI Audits: none requested by the Division and none done voluntarily by DSI.

DDMAC: As of June 3, 2003, DDMAC had not submitted a review for this application.

Debarment Certification: included in package

OPDRA Tradename Review: The applicant's proposed tradename of Benicar HCT was found acceptable by ODS on October 10, 2002, and found to be acceptable on re-review on April 15, 2003.

Comments: A telecon was held with the sponsor on May 27 and June 2, 2003 to discuss revisions the Division proposed for the labeling. At the June 2, 2003 telecon Sankyo and the Division agreed to labeling text to be attached to the approval letter. In the approval letter, the sponsor will be requested to submit final printed labeling at their next printing.

/S/

Edward J. Fromm

dr-ef-6-3-03

44 Draft Labeling Page(s) Withheld

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5365, FAX (301) 594-5494

Divisional Memorandum

DATE: 5.28.03

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 21-532
NAME OF DRUG: Benicar HCT (Olmesartan medoxomil-Hydrochlorothiazide) Tablets
SPONSOR: Sankyo Pharma., Inc.

DOCUMENTS USED FOR MEMO:

1. Medical Reviews by Salma Lemtouni, M.D., dated 5.8.03 and Maryann Gordon, M.D., dated 2.28.03.
2. Secondary Medical Review by Avi Karkowsky, M.D., dated 4.3.03 and 4.23.03.
3. Chemistry Reviews by Monica D. Cooper, Ph.D., dated 4.3.03 and 4.23.03 (Reviews #1 and 2 respectively).
4. Clinical Pharmacology and Biopharmaceutics Review by B. Nhi Nguyen, Pharm.D., dated 4.10.03.
5. Statistical Review of Clinical Data by James Hung, Ph.D., dated 1.30.03.
6. Pharmacology Review by Gowra Jagadeesh, Ph.D., dated 3.27.03.
7. Proprietary Name review by Charlie Hoppes, R.Ph., M.P.H., Division of Medication Errors and Technical Support (DMETS), dated 4.15.03. Benicar was viewed as acceptable.
8. Proposed Vasopran labeling and comments on labeling by Dr. Karkowsky.
9. Establishment Evaluation Requests for 7 manufacturing sites, all approved by District Office.
10. Debarment Certification dated 7.9.02 from sponsor.
11. No DSI audits were requested or performed.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum decision of an approvable action for the NDA named above for Olmesartan Hydrochlorothiazide (HCTZ) as an antihypertensive. If labeling can be agreed to an approval action is justified. The optimal doses are likely wider than those proposed for marketing, but three doses proposed provide the low and high-dose combinations of the two products (20/12.5 and 40/25 mg of olmesartan and HCTZ respectively) currently marketed, and the dose-dependent adverse effects are monitorable and symptomatic, such that the proposed range to be marketed is acceptable.

BACKGROUND AND OVERVIEW

The reviewers of the clinical data all agree that the combination of the two products lowers blood pressure and that when used together, both products contribute to the efficacy (essential for a combination product development of this type). Dr. Hung concluded that for sitting DBP, the combination of olmesartan and HCTZ is more effective than either of the monotherapies at each of the dose combinations studied in the pivotal trial (olmesartan 10, 20 and 40 mg, HCTZ 12.5 and 25 mg). Indeed, he concludes that there is evidence of 'superadditivity', as the combination has greater effects than the sum of the two components used alone (although this was not significant, see his discussion page 6 of his review). I interpret his surface map (figure 2 in his review) to support the idea that for olmesartan, 20

and 40 mg doses are similar in their effects on BP, either alone (from monotherapy NDA) or when used in combination with HCTZ, It is also clear that the 10 mg dose had robust efficacy alone and in combination with HCTZ. The map also shows that HCTZ 25 mg has greater BP lowering effect than 12.5 mg, both alone and in combination with olmesartan. As regards safety, Dr. Gordon correctly points out the relatively small database for this product (1243 patients) but given the available data no new safety concerns were identified and the product's safety has been characterized sufficiently. In particular, there is no signal for increased renal toxicity or hyperkalemia when the combination is used.

CHEMISTRY

Drug Substance
The Chemistry reviewer, Dr. Cooper, identified no deficiencies in drug substance. The current data will support a shelf life of 18 months.

Drug Product
No deficiencies were identified.

Container/Closure
No deficiencies were identified.

Environmental Assessment
The environmental assessment (Chemistry review #1, page 50) was considered acceptable.

Microbiology
Not Applicable (oral preparation).

cGMP Inspections
No deficiencies were identified and 7 sites were approved.

PRE-CLINICAL PHARMACOLOGY TOXICOLOGY

A number of non-clinical Pharm/Tox studies were submitted and reviewed Dr. Jagadeesh. This includes single and multi-dose toxicology studies up to 26 weeks in rats and dogs, genotoxicity in two in vitro models and one in vivo mouse model and developmental toxicity in pregnant mice and rats. No pharmacokinetic interaction between the two products was noted and the two drugs had their anticipated pharmacologic effects when combined. As seen with the olmesartan monotherapy, the animals exhibited a dose-dependent incidence of progressive renal injury ('Chronic Progressive Nephropathy') but there was no evidence of an interaction with HCTZ to augments the toxicity.

The genotoxicity findings are relevant, especially given the amount of attention paid to the potential carcinogenicity of olmesartan during its review. The findings did not suggest any interaction with HCTZ to augment any genotoxicity (and most of the assays were negative for olmesartan-HCTZ, see review for details).

For reproductive toxicity (Seg 2), in mice there was no evidence for either maternal or developmental toxicity for the combination at doses up toe 1000/635 mg/kg/day for olmesartan/HCTZ respectively. In rats, there was evidence of stomach erosions and weight loss only at the highest dose studied, an effect more than likely due to the physical volume of drug not effect.

The reviewer made one recommendation regarding the description of these findings in the label as proposed by the sponsor.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The Clinical Pharmacologist, Dr. Nguyen, reviewed three bioequivalence studies linking the drug used in the clinical trials to the proposed marketed formulations (20/12.5, 40/12.5 and 40/25 for olmesartan/HCTZ respectively). Her recommendation is that the biowaiver be granted for these three strengths, given the following:

Linear PK over the concentration range of the three combinations.
Composition proportionality between the 40/12.5 and 40/25 tablets.
Comparable dissolution profiles in three media, and
Bioequivalence of the individual formulations.

For the bioequivalence testing, it's worth noting that the — dose did not demonstrate bioequivalence at Cmax for the comparison between the to-be-marketed formulation and the tablets used in the U.S. enrollees in the pivotal factorial trial (see Dr. Nguyen's review, table11). That only the peak falls out of spec is acceptable, and unlikely to have clinical consequence, although why the two formulation comparisons (U.S., O.U.S.) would be that different is something of a mystery.

Dr. Nguyen asserts that no food-effect study was done, and that none was needed given the fact that food did not affect the monotherapies, based on earlier data from the original NDA. Apparently, the Division has not routinely been concerned about this potential interaction, even for drugs with low bioavailability like olmesartan.

Specific dissolution method/specifications were recommended, as usual (see page 2 of Dr. Nguyen's review for details).

MEDICAL/STATISTICAL REVIEW

Antihypertensive Efficacy

The reviewers of the clinical data all concluded that Olmesartan/HCTZ has demonstrated antihypertensive efficacy sufficient for approval as a combination product.

Dose-Response Relationship For Olmesartan/ HCTZ

Dr. Hung has analyzed the dose-response in two ways in his review and by either metric the product is approvable as a combination. Dr. Karkowsky asserts that because the addition of 20 or 40 mg of olmesartan to 12.5 of HCTZ was not significantly superior to both the components separately that these lower doses might not 'meet' the requirements for a combination. While supportive of his view that the marketed doses of olmesartan are not significantly different in terms of their effects on diastolic BP, it is apparent from table 2 of Dr. Hung's review that the two products are additive, and the lack of statistical significance is more likely a product of size than a reflection of a pharmacodynamic interaction between the two drugs affecting their BP effects when used together.

The secondary analyses (sitting SBP, standing DBP and SBP) reinforce the conclusions above.

Dose-Response Relationship For Olmesartan as Monotherapy

Olmesartan is currently marketed in 5, 20 and 40 mg dose strengths. The 5 mg dose is intended for use by individuals who are volume-contracted or otherwise at risk of hypotension with initial dosing. At the time of the monotherapy approval there was significant discussion around the appropriate low dose to recommend starting olmesartan. The data in this NDA reinforce the view that the 10 mg strength was the best starting dose (absent good data on lower doses). In Dr. Hung's review, the changes in sitting DBP for 10, 20 and 40 mg doses (without HCTZ) were -13.1, -12.7, and -14.4 respectively (table 2). The data also reinforce the view that there is very little to distinguish the efficacy of the 10, 20 and 40 mg doses.

Special Populations

The statistical reviewer summarized the BP effects of olmesartan/HCTZ in the relevant demographic populations. While sufficient males and females were enrolled, and no differences in overall efficacy and safety observed, too few subjects >65 and non-White were enrolled to be informative of any relevant differences in efficacy (see Dr. Lemtouni's review, page 11 for the demographics of the pivotal trial).

Safety

Dr. Gordon reviewed the safety, and the reader is referred there for details. No novel safety concerns were identified in a population of 1243 patients. Importantly, no signal for increased renal toxicity or for an increase in abnormalities in potassium were identified.

SUMMARY

Olmesartan/HCTZ has been adequately characterized to approve as a combination therapy for use in the treatment of hypertension for individuals who do not respond to monotherapy with one of its components. The ideal combinations to be marketed would include a 10 mg olmesartan combination based on the data submitted in the NDA. This combination would provide an effective option for patients starting olmesartan after reaching 25 mg of HCTZ. This dose combination is not currently proposed by the sponsor. The argument would be that starting at the lower dose of olmesartan would decrease the incidence of dose-related adverse events. In this database, dizziness appears to be the only dose-related adverse event, undermining to some extent the power of this argument (that is, a symptomatic and

monitorable adverse event). Additionally, the three combinations proposed by the sponsor will provide some, but not all of the combinations, as has been pointed out by Dr. Karkowsky, and an individual on HCTZ 25 mg will not have an option to start on 20 mg of olmesartan as the next step (but will have the option of the 40/12.5 mg combination if necessary).

Labeling Comments

The label needs to be revised to reflect more standard language we have used in other labels to emphasize the second-line nature of the recommended use of this product (mirroring, say, the language used in telmisartan/HCTZ or eprosaratan/HCTZ).

The inadequate enrollment of non-White and elderly individuals should be reflected in the label.

The label needs to include the changes recommended by Pharm-Tox.

The language on the long-term efficacy of the product seems over-stated and should be revised or eliminated until more robust data are available.

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/s/

Doug Throckmorton
5/27/03 12:53:45 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: April 29, 2003

FROM: Abraham Karkowsky, M.D., Ph.D. Group Leader, Division of Cardio-Renal Drug Products HFD-110

THROUGH: Dr. Douglas Throckmorton, Director, Division of Cardio-Renal Drug Products (HFD-110)

SUBJECT: Approvability of Benicar HCT ™ (olmesartan medoxomil/ hydrochlorothiazide combination, NDA 21-532; IND [redacted]

The combination product olmesartan medoxomil (olmesartan, CS-866) with hydrochlorothiazide tablets is approvable for the treatment of hypertension. The sponsor requested approval of the following strengths of olmesartan/hydrochlorothiazide: 20/12.5, 40/12.5 and 40/25. The combination product at these doses can be used as a substitute for the individual products when the product corresponds to the titrated doses. The product can also be used if, after titration to the highest dose of olmesartan, additional blood pressure effect is desired. A marked–up copy of labeling, tracked through all reviewers, has been forwarded to Ed Fromm, the project manager.

For those initially treated with hydrochlorothiazide to a 25-mg dose, [redacted]

The documents utilized for this review consist of:

- Medical officer review- efficacy: Salma N. Lemtouni, M.D., dated 10 April 2003.
- Medical officer review-safety: Maryann Gordon, M.D., dated 28 February 2003.
- Statistical review and evaluation: James Hung, Ph.D., dated 30 January 2003.
- Clinical pharmacology and biopharmaceutics review: B. Nhi Nguyen, Pharm.D., dated 10 April 2003.
- Pharmacology review: G. Jagadeesh, Ph.D., dated 27 March 2003.
- Chemistry reviews: Monica D. Cooper, Ph.D., dated 3 April 2003 and 23 April 2003.
- Office of drug safety review: Charlie Hoppes, R. Ph., M.P.H, dated 9 April 2003.
- Division of medication errors and technical support: Kevin Derminoski, R.Ph. dated 25 October 2002.

No DSI audits were requested and no reports were submitted. Inspections of all manufacturing establishments have been completed and were acceptable. The requirement for environmental assessments was waived.

Benicar HCT was acceptable to DMETS. DMETS expressed some concern that the combination product could be confused with Benicar monotherapy and suggests the following be transmitted to the sponsor:

- The labeling of Benicar HCT should be differentiated from Benicar by using contrasting design, color, boxing or some other means.
- The unit measure should be listed with the amount of each ingredient in the product. For example, "[redacted] should be revised to read "20 mg/12.5 mg".
- The strength of the product should be located in conjunction with the established name.

In addition, DMETS suggests that the bottles, which contain 30 and 90 tablets, be supplied with child resistant closure. DMETS also requests submission of the complete set of container and carton labeling for review.

With respect to financial disclosures, the sponsor submits form # 3454 in which the sponsor asserts that no financial arrangements were entered into with any clinical investigator. The form also states that no clinical investigators entered into a financial arrangement for which the compensation to the investigator would be dependent on the outcome of the study.

Our chemists suggest an expiration date of 18 months for the product whether packaged in DDPE bottles or Aluminum/Aluminum blisters. The Division's biopharmaceutics and chemists recommend the following dissolution specifications. Dr. Nguyen has transmitted these specifications to the sponsor. These dissolution specifications as well as the expiration date should be transmitted within the approvable letter.

Olmesartan (CS-866)

Medium:	900 ml, JP fluid 2 pH 6.8 37°C
Apparatus:	USP II (paddle)
Speed:	50 RPM
Specification:	Q not less than [redacted] at 45 minutes

Hydrochlorothiazide

Medium:	900 ml, JP fluid 2 pH 6.8 37°C
Apparatus:	USP II (paddle)
Speed:	50 RPM
Specification:	Q not less than [redacted] at 15 minutes

Olmesartan is currently approved for once daily dosing at either 20 or 40 mg once daily. Hydrochlorothiazide is approved with the usual lowest dose of 12.5 mg. Doses greater than 25 mg daily not generally used. The efficacy of combination products is supported by the single large factorial study (# CS-866-318). In this study 48 sites enrolled 502 patients (500 were evaluable) who were randomized to receive one of 12 treatments in this 3 x 4 factorial study. The three doses of hydrochlorothiazide were 0, 12.5 and 25 mg. The four doses of olmesartan were 0, 10, 20 and 40 mg once daily. The change in sitting diastolic blood pressure (last observation carried forward for those who prematurely discontinued) at interdosing interval are shown in Table 1.

Table 1. Baseline subtracted sitting diastolic blood pressure effect (mean ± se)

		Olmesartan (mg)			
		0	10	20	40
HCTZ (mg)	0	-7.7 ± 1.2 (n=42)	-13.1± 1.3 (n=39)	-12.7± 1.3 (n=41)	-14.4± 1.3 (n=45)
	12.5	-9.1 ± 1.2 (n=45)	-15.3 ± 1.4 (n=35)	-15.4 ± 1.4 (n=42)	-18.0 ± 1.5 (n=42)
	25	-12.9 ± 1.3 (n=43)	-18.4 ± 1.2 (n=38)	-18.9 ± 1.1 (n=46)	-21.9 ± 1.5 (n=39)

The AVE test for unequal cell sizes (Hung; 2000, Statistics in Medicine p 2079-2087) was highly significant $p < 0.001$, indicating that at least one of the combinations was superior to its individual components.

The ANOVA analysis of the data indicated that the combination products, at each of the tested doses, were superior to the individual components.

An analysis of the response surface indicates progressive increase in effect as the dose of hydrochlorothiazide is increased. As the dose of olmesartan increases the effect levels off (the quadratic term for olmesartan in the response surface function was highly significant).

Other measurements of trough blood pressure effect, sitting systolic (Table 2), standing diastolic (Table 3) or standing systolic (Table 4) blood pressure consistently demonstrate that the combination product is superior to each of the components.

Table 2. Baseline subtracted sitting systolic blood pressure effect (mean ± se)

		Olmesartan (mg)			
		0	10	20	40
HCTZ (mg)	0	-3.4 ± 1.9 (n=42)	-10.4± 1.8 (n=39)	-15.2± 2.5 (n=41)	-16.4± 2.1 (n=45)
	12.5	-8.2 ± 2.1 (n=45)	-20.3 ± 2.2 (n=35)	-20.4 ± 2.6 (n=42)	-19.4 ± 2.6 (n=42)
	25	-17.6 ± 2.0 (n=43)	-22.9 ± 2.3 (n=38)	-25.7 ± 1.9 (n=46)	-27.9 ± 2.5 (n=39)

Table 3. Baseline subtracted standing diastolic blood pressure effect (mean ± se)

		Olmesartan (mg)			
		0	10	20	40
HCTZ (mg)	0	-6.1 ± 1.3 (n=42)	-10.0± 1.1 (n=39)	-11.0± 1.3 (n=41)	-12.6 ± 1.2 (n=45)
	12.5	-8.6 ± 1.2 (n=45)	-13.2 ± 1.4 (n=35)	-15.8 ± 1.3 (n=42)	-15.6 ± 1.6 (n=42)
	25	-9.6 ± 1.2 (n=43)	-16.6 ± 1.0 (n=38)	-15.8 ± 1.1 (n=46)	-20.3 ± 1.6 (n=39)

Table 4. Baseline subtracted standing systolic blood pressure effect (mean ± se)

		Olmesartan (mg)			
		0	10	20	40
HCTZ (mg)	0	-4.8 ± 1.6 (n=42)	-11.9± 1.7 (n=39)	-11.8± 2.2 (n=41)	-16.4± 2.1 (n=45)
	12.5	-9.7 ± 2.1 (n=45)	-19.6± 2.5 (n=35)	-20.4 ± 2.7 (n=42)	-18.9 ± 2.4 (n=42)
	25	-14.7 ± 2.1 (n=43)	-21.5 ± 2.2 (n=38)	-24.4 ± 2.1 (n=46)	-29.0 ± 2.3 (n=39)

With respect to demographic subgroups, the effect in males and females were similar. There were relatively few subjects in each treatment group > 65 years old (ranging from 7-21 %), relatively few blacks (ranging from 7-28%) or race classified as other (ranging from 8-17%) to adequately assess whether the effects differ in these subgroups from the population as a whole.

Safety of the combination product is derived from the one pivotal factorial design study (# CS-866-318). This database represents the only information for comparative and dose related adverse events.

In addition, there were non-randomized cohorts that had hydrochlorothiazide added when blood pressure was not adequately controlled by olmesartan monotherapy or who entered an open-label extension of the placebo-controlled factorial study. There were also a small number of subjects who were enrolled into a positive control (atenolol) study on a base 25-mg of hydrochlorothiazide. These cohorts are useful in describing rare and serious events. There were a total of 1292 hypertensive subjects who received olmesartan medoxomil and hydrochlorothiazide (1243 patients) or olmesartan medoxomil plus hydrochlorothiazide plus amlodipine (49 patients). Of the patients who received olmesartan and hydrochlorothiazide, 316 were treated for 6 or more months and 112 for at least one year.

With respect to the factorial design studies, there were few subjects who discontinued. For each of the groups, there were 0 to 2 subjects who discontinued for adverse events (no placebo patient discontinued for adverse events). The most frequent reason for discontinuation from treatment with the combination products were hypotension, dizziness, palpitations or combinations of the above. One subject discontinued from the 40-mg olmesartan/25-mg hydrochlorothiazide dose for dizziness and syncope. One subject in the olmesartan 10-mg monotherapy discontinued due to elevated liver enzymes (these were elevated at baseline).

The number of subjects with > 3 events in any group is shown below. The overall frequency of adverse does not appear substantially different with the exception of dizziness that appears more prominent at the highest combination relative to placebo. The frequency of dizziness also increases as the dose of either HCTZ or olmesartan increase.

Table 5. % of subjects in study # CS-866-318 with adverse events

	HCTZ=0 mg				HCTZ =12.5 mg				HCTZ = 25 mg			
Olmesartan	0	10	20	40	0	10	20	40	0	10	20	40
# patients with any	52%	43%	51%	42%	44%	46%	50%	55%	44%	56%	45%	50%

Headache	7%	5%	15%	7%	4%	9%	11%	5%	5%	3%	4%	0%
Upper Respiratory Tract Infections	0%	5%	5%	9%	4%	0%	9%	9%	9%	8%	9%	3%
Dizziness	2%	0%	2%	7%	7%	3%	7%	9%	9%	13%	9%	15%
Abdominal Pain	2%	0%	5%	4%	2%	0%	0%	0%	0%	3%	6%	3%
Nausea	0%	3%	2%	0%	0%	0%	2%	2%	2%	8%	0%	5%
Myalgia	0%	5%	2%	2%	2%	0%	2%	0%	0%	8%	2%	0%

With respect to laboratory abnormalities, more subjects who were normal at baseline, had values exceeding an upper normal value (in parenthesis) at week 8, on the combination product for : BUN (> 24 mg/dL), creatinine (> 1.2, > 1.1 mg/dl for males and females, respectively) and uric acid (> 7.5 mg/dL). One subject on 10-mg olmesartan monotherapy 10 mg discontinued because of abnormal liver function enzymes.

In considering hematology, hematocrits and hemoglobin were lower on combination, largely related to the use of olmesartan. At the 40-olmesartan /25-hydrochlorothiazide dose the median change in hemoglobin was-0.7 g/dl. There was a median change of +0.2 g/dl in the placebo group. Hematocrit changes ranged from -1% in the placebo group to –3% for the olmesartan-40 mg/25 mg hydrochlorothiazide.

Long-term exposure indicated no frequent and unusual rare adverse events likely to be attributable to the combination product.

Biopharmaceutical considerations:

Bioequivalence was established between the tested formulation and the to-be – marketed and the monotherapies which were used in clinical trials for the 20-mg olmesartan/12.5-mg hydrochlorothiazide and Bioequivalence for the 40-mg olmesartan/25-mg hydrochlorothiazide was waived because of composition proportionality to the to-be-marketed 20-mg olmesartan/12.5-mg hydrochlorothiazide, which was bioequivalent to the individual components.

Table 6. Bioequivalence status of olmesartan/hydrochlorothiazide combinations.

		Olmesartan (mg)		
		10	20	40
HCTZ (mg)	12.5	Not studied	Bioequivalent	Bioequivalent
	25	Not studied	Not bioequivalent	Waived

The formulation was not bioequivalent to the components used in the clinical trials. The confidence intervals of the Cmax for hydrochlorothiazide was below the 80% accepted cut off for bioequivalence. The AUC, however, was well within the acceptable range for bioequivalence. Approval of this formulation strength, though not strictly bioequivalent, would appear reasonable pending additional stability testing. The , may be particularly useful for those unsuccessfully treated with hydrochlorothiazide. Additional bioequivalence study as well as additional stability studies would be necessary to approve this dose strength.

In summary, the proposed dose strengths of olmesartan/hydrochlorothiazide: 20/12.5, 40/12.5 and 40/25 should be approved, a dosing strength of 10/25 would be a useful adjunct to hypertension treatment but would require a bioequivalence study and additional stability data.

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/s/

Abraham Karkowsky
5/7/03 11:33:20 AM
MEDICAL OFFICER

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/s/

Doug Throckmorton
6/5/03 08:14:14 AM

Office of Drug Safety

Memo

To: Douglas Throckmorton, M.D.
Director, Division of Cardio-Renal Drug Products, HFD-110

From: Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support
Office of Drug Safety, HFD-420

CC: Edward Fromm
Project Manager, Division of Cardio-Renal Drug Products
Office of Drug Evaluation I, HFD-110

Date: April 9, 2003

Re: ODS Consult 02- 0169-1; Benicar HCT (Olmesartan Medoxomil and Hydrochlorothiazide) Tablets; NDA 21-532

This memorandum is in response to a March 21, 2003, request from your Division for a re-review of the proprietary name, Benicar HCT.

Since the completion of our initial review of the proprietary name Benicar HCT, conducted on October 10, 2002 (ODS consult 02-0169), DMETS has identified one additional proprietary name, Benoquin, as having the potential to cause name confusion with Benicar HCT.

Benoquin (Monobenzone Cream) 20% is indicated as a depigmenting agent primarily in patients with vitiligo. Benoquin Cream is applied once or twice daily to the affected areas. Benicar and Benoquin may sound similar when spoken. The names each have three syllables. The first two syllables, "Beni" vs. "Beno" are very similar, slightly differing in the short vowels "i" vs. "o". The last syllable, "car" vs. "quin" also have similar sounds due to the "c" sound which may sound like "qu". The products Benicar and Benoqin have many differences. Benicar is a tablet for once daily oral administration while Benoquin is a topical cream to be used once or twice daily. The strength of Benicar may also serve to differentiate the products since Benicar is expressed in terms of the combined active ingredients (20 mg/12.5 mg, 40 mg/12.5 mg, or 40 mg/25 mg) while Benoquin is expressed as 20% monobenzone. Additionally, Benoquin had low recorded sales in the year 2002 according to the Saegis Pharma[1] database. Most likely Benoquin is not kept in stock on pharmacy shelves and would therefore require a special order. The limited availability of Benoquin would act as a barrier to product confusion with Benicar. Finally, a search of the FDA Adverse Reporting System (AERS) for post-marketing safety reports of medication errors associated with the names Benicar and Benoquin did not identify any cases of name confusion. Therefore, given the differences in dosing, dosage form, strength, route of administration, low availability of Benoquin, and a lack of errors associated with the name Benicar, the risk of confusion between Benicar HCT and Benoquin is minimal.

In summary, identification of the proprietary name Benoquin, is not sufficient to overturn our initial decision of recommending the proposed proprietary name Benicar HCT. ODS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary/established names from this date forward.

Additionally, in DMETS' Consult # 02-0169 dated October 10, 2002, recommendations were made to address safety concerns regarding the labeling and packaging of Benicar HCT. The Division Project Manager states that the sponsor has not yet been made aware of these recommendations but that the comments will be taken into consideration when the Division sends an approvable letter. DMETS continues to recommend implementation of the labeling revisions outlined in Consult #02-0169 and requests that the Division forward revised container labels and carton labeling for review when they are available.

If you have any questions or need clarification, please contact Sammie Beam, Project Manager, at 301-827-3242.

[1] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com.

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/s/

Charles Hoppes
4/15/03 11:33:50 AM
PHARMACIST

Alina Mahmud
4/15/03 01:33:53 PM
PHARMACIST

Carol Holquist
4/15/03 01:58:00 PM
PHARMACIST

MINUTES OF A TELECONFERENCE

NDA 21-532
Submission Date: August 5, 2002
Drug Name: ~~Benicar HCT~~ (Olmesartan/Hydrochlorothiazide)
Sponsor: Sankyo Pharma Inc

Date: September 20, 2002
Attendees:

	FDA	Nhi Nguyen, Pharm.D., Clin Pharm & Biopharm Reviewer
		Patrick Marroum, Ph.D., Team Leader
		Roshni Ramchandani, Ph.D., Intern
	Sponsor	Albert Yehaskel, Senior Director, RA
		Donald Hinman, Ph.D., Senior Director, Clinical Development
		Lisette Gonzalez, Manager, Clinical Development

The purpose of the teleconference was to discuss the two studies that the Agency feels the sponsor needs to market the strengths of olmesartan /HCTZ , 20/12.5, 40/12.5, and 40/25 mg.

Summary of Minutes

The sponsor stated that they only intend to market three strengths of olmesartan/HCTZ: 20/12.5, 40/12.5 and 40/25 mg. I told them that the only additional study needed would be a bioequivalence study linking the 40/12.5 mg tablet if the sponsor only wants to market those three strengths. Regarding the 20/12.5 mg and 40/25 mg tablets, the sponsor has conducted a bioequivalence study for the 20/12.5 mg tablet and is requesting a waiver for the 40/25 mg tablet. The sponsor has submitted appropriate dissolution data in three media. We told the sponsor that the Agency usually does not waive up. However, if the formulation for the 20/12.5 and 40/25 mg are compositionally similar and the pharmacokinetics are linear, the Agency would grant a waiver for the 40/25 mg tablet if the data are supportive.

We told the sponsor that they need to provide a link between the formulations used in the clinical trials (separate entities) and the to-be-marketed formulations. The summary of this discussion is provided in the overall summary below.

The sponsor stated that the 20/12.5 mg and the 40/25 mg tablets are made
The tablets are made
We asked them for the *in-vivo* study for

The sponsor cited a dose proportionality study, 866-127. This was a study that evaluated the dose proportionality of olmesartan and the bioequivalence of HCTZ. The combination tablets of 20/12.5 and 40/12.5 mg were tested. This study found that the olmesartan strengths are dose proportional and the HCTZ' are bioequivalent. We examined the 90 % confidence intervals to see if they met the bioequivalence criteria and the Cmax did not. Additionally, the criteria were wider than the accepted 0.80 to 1.25.

We pointed the sponsor to page 12 of the BA/BE Guidance on the FDA website. We asked the sponsor if the formulations met one of the two criteria for a waiver. It was concluded that the formulations do not because the active and inactive ingredients are not in exactly the same proportion between the different strengths. Additionally, the second criteria is applicable for low potency dosage forms (< 5 mg), which Benicar HCT is not.

Overall Summary

1. The sponsor can obtain a waiver for the 40/25 mg tablet. This can be achieved if the pharmacokinetics are linear, the 20/12.5 mg tablet is compositional similar, and the 20/12.5 mg combination is bioequivelant to the separate entities (study 866-108).

2. The sponsor needs to conduct a bioequivalence study linking the formulations used in the clinical trial (the two separate entities) and the to-be-marketed formulation.

a. If the sponsor intends to market the 40/12.5 mg tablet, the sponsor must do a bioequivalence study to link the 40/12.5 to-be-marketed formulation and the separate entities (e.g., olmesartan 40 mg and HCTZ 12.5 mg).

b. If the sponsor does not market the [redacted] tablet and wants to market the [redacted] tablet, then the sponsor must do a bioequivalence study to link the [redacted] formulation and the separate entities (e.g., olmesartan [redacted] and HCTZ [redacted] g).

c. If the sponsor does not market the [redacted] tablet and wants to market the [redacted] tablet then the sponsor must do a bioequivalence study to link the [redacted] formulation and the separate entities (e.g., olmesartar [redacted] and HCTZ [redacted]).

d. If the sponsor intends to market both the [redacted] tablets, then the sponsor can conduct one bioequivalence study with the [redacted] tablet and with supportive data obtain a waiver for the [redacted] tablet.

3. The bioequivalence studies will not hold up the review clock and will not affect the approvability of the drug. It may affect the marketing of the drug depending on when the studies are submitted to the Agency.

4. The sponsor would like to discuss today's teleconference internally and will get back to us next week with how they will proceed.

→ of each component?

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA 21-532, Benicar HCT (olmesartan medoxomil/hydrochlorothiazide) Tablets, ——, 20/12.5mg, 40/12.5 mg, and 40/25 mg.

Applicant: Sankyo Pharma

Date of Application: August 5, 2002
Date of Receipt: August 5, 2002
Date of Filing Meeting: September 11, 2002
Filing Date: October 5, 2002

Indication(s) requested: Treatment of Hypertension

Type of Application: Full NDA __X_____ Supplement _____
(b)(1) ____X_____ (b)(2) _____

Therapeutic Classification: S___X____ P_____
Resubmission after a withdrawal or refuse to file __NA_____
Chemical Classification: (1,2,3 etc.)__4____
Other (orphan, OTC, etc.)___NA_____

Has orphan drug exclusivity been granted to another drug for the same indication? NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
NO

If the application is affected by the application integrity policy (AIP), explain. NO

User Fee Status: Paid ____X_____ Waived (e.g., small business, public health) _____
Exempt (orphan, government) __NA_____
Form 3397 (User Fee Cover Sheet) submitted: YES___X____ NO_____
User Fee ID#____4366_____
Clinical data? YES ___X____ NO _____ Referenced to NDA# _____
Date clock started after UN ____NA_____

User Fee Goal date: ___June 5, 2003_____

Action Goal Date (optional) ___June 5, 2003_____

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.
- Submission complete as required under 21 CFR 314.50? YES
- If electronic NDA, does it follow the Guidance? YES
  If an electronic NDA: all certifications must be in paper and require a signature.
- If Common Techinical Document, does it follow the guidance? NA

- Patent information included with authorized signature? YES

- Exclusivity requested? YES; If yes, ___3____years

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? NO (requested waiver for all age groups)

- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

List referenced IND numbers: IND ——

End-of-Phase 2 Meeting? NO, but a meeting to discuss study design was held on February 16, 2000

Pre-NDA Meeting(s)? NO

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? YES

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? NA

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? NA

Advisory Committee Meeting needed? NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
  If no, did sponsor submit a complete environmental assessment? NA
  If EA submitted, consulted to Nancy Sager (HFD-357)? NA

- Establishment Evaluation Request (EER) package submitted? YES

- Parenteral Applications Consulted to Sterile Products (HFD-805)? NA

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 11, 2002

BACKGROUND

Olmesartan medoxomil, NDA 21-286, was approved on April 25, 2002 for the treatment of hypertension. Sankyo submitted this NDA, 21-532, for a combination of olmesartan medoxomil and hydrochlorothiazide for the treatment of hypertension. The other six approved angiotensin II blockers also have combinations with hydrochlorothiazide that have been approved.

Olmesartan/hydrochlorothiazide has not been marketed in any other country.

ATTENDEES:

Douglas C. Throckmorton, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader
Maryann Gordon, M.D., HFD-110, Medical Officer
Salma Koessel, M.D., M.P.H., HFD-110, Medical Officer
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Nhi Nguyen, Pharm.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Gowra Jagadeesh, Ph.D., HFD-110, Pharmacologist
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
Kasturi Srinivasachar, Ph.D., HFD-810, Team Leader, Division of New Drug Chemistry I
Robert Shibuya, M.D., HFD-47, Division of Scientific Investigations
Edward Fromm, HFD-110, Regulatory Health Project Manager

ASSIGNED REVIEWERS:

Discipline	Reviewer	Expected
Medical (Safety):	Maryann Gordon, M.D.	2/28/03
Medical (Efficacy):	Salma Koessel, M.D., M.P.H.	3/31/03
Secondary Medical:	Abraham Karkowsky, M.D., Ph.D.	4/30/03
Statistical:	James Hung, Ph.D.	1/31/03
Pharmacology:	Gowra Jagadeesh, Ph.D.	2/28/03
Statistical Pharmacology:	NA	
Chemist:	Monica Cooper, Ph.D.	2/28/03
Environmental Assessment (if needed):	Monica Cooper, Ph.D.	2/28/03
Biopharmaceutical:	Nhi Nguyen, PharmD.	3/31/03
Microbiology:	NA	
DSI:	Robert Shibuya, M.D.	4/30/03 (if needed)
Project Manager:	Edward Fromm	
Other Consults:	NA	

Per reviewers, all parts in English, or English translation? YES__X___ NO___

CLINICAL – File ___X_____ Refuse to file _____

- Clinical site inspection needed: YES_? (Dr. Karkowsky to see if any sites should be inspected)

MICROBIOLOGY CLINICAL – File___NA_____ Refuse to file_____

STATISTICAL – File ___X_____ Refuse to file _____

BIOPHARMACEUTICS – File ___X_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X_____

PHARMACOLOGY – File ___ X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? YES__X___NO_____ File__X___ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

___X____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

The deficiencies identified at the meeting (but not causing RTF) were the need for bioequivalence studies for the ——— 40/12.5 mg strengths if the sponsor wants to market all ——— strengths.

_____ The application is unsuitable for filing. Explain why:

_____
Edward Fromm, Regulatory Health Project Manager, HFD-110

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Doug Throckmorton
9/26/02 01:47:07 PM

Minutes of a Meeting between Sankyo Pharma and the FDA

Date: February 16, 2000

Sponsor: Sankyo Pharma Inc.

Subject: CS-866/HCTZ for hypertension

Type of Meeting: Guidance

FDA Participants:

Raymond Lipicky, M.D., HFD-110, Director, Division of Cardio-Renal Drug Products
Robert R. Fenichel, M.D., Ph.D., HFD-110, Deputy Division Director
Shari Targum, HFD-110, Medical Officer
Gowra Jagadeesh, HFD-110, Pharmacologist
Charles Resnick, Ph.D., HFD-110, Pharmacology Team Leader
James Hung, Ph.D., HFD-110, Statistician/Team Leader
Emmanuel Fadiran, Ph.D., HFD-860, Clinical Pharmacologist and Biopharmaceuticist
Julie Canal, Biopharmaceutics Fellow
Edward Fromm, HFD-110, Consumer Safety Officer

Sankyo

David Woodward, Ph.D. (Senior Vice President, Development, Sankyo USA Development, Division of Sankyo Pharma, Inc.)
Donald Hinman, Ph.D. (Director, Clinical Research, Sankyo USA Development, Division of Sankyo Pharma, Inc.)
Antonia Wang, Ph.D. (Director, Statistics, Sankyo USA Development, Division of Sankyo Pharma, Inc.)
Mr. Hisashi Nakagaki, Manager of Clinical Research
Albert Yehaskel, MS, MBA (Associate Director, Regulatory Affairs, Sankyo Pharma Inc.)

Background

Sankyo is planning to develop a combination product consisting of CS-866, an angiotensin II receptor antagonist, and HCTZ (hydrochlorothiazide). The company is seeking guidance from the Division on how to proceed with development of the combo product.

The company has a monotherapy component, CS-866, which is [redacted] The studies for the combo product will be conducted under the IND for CS-866, IND [redacted]

Meeting

Trial Design

The firm opened the meeting by noting that they had a monotherapy component, CS-866, under development and wanted to discuss proposed studies for a combination of CS-866 and HCTZ.

Dr. Lipicky asked the firm what the upper dose of CS-866 was. The firm said that they were studying a dosing range of 10-40 mg for the CS-866 and a range of 12.5-25 mg for HCTZ. They added that they were planning to do one phase 3 factorial study and one bioequivalence study with the combination product. Dr. Lipicky said the firm's proposed studies were acceptable but suggested that more information could be gained if the company studied doses of 3, 10, and 40 mg for CS-866 and 6.25-25 mg of HCTZ. The firm noted that they had not proposed a 6.25 mg dose of HCTZ because other competitors had tried that dose and noted very little dose response.

Mutagenicity

Dr. Lipicky mentioned that mutagenicity of CS-866, although not discussed at a 1997 meeting with the firm, had surfaced as a major problem with this compound. He noted that the compound is positive for mutagenicity in the in-vitro tests. The firm said that they believed that the cause of the mutagenicity was a putative metabolite, not the active metabolite of the drug and not the parent compound. They noted that they had conducted a 2 year rat carcinogenicity study and a 26 week transgenic mouse carcinogenicity study and had not found any evidence of carcinogenicity. Dr. Lipicky said, although the carcinogenicity studies provided a little reassurance, he would still have to weigh the risks of the compound with the potential clinical benefit of the drug. He noted that mutagenicity is an uncertain risk and one that poses a major obstacle in approving the drug. Dr. Fenichel said this situation reminded him of tasosartan, a drug that was associated with hepatic enzyme elevations. The Agency thought that the hepatic enzyme elevations were probably not indicative of serious liver injury but nevertheless thought it was unwise to approve the drug when other sartans with fewer side effects were available to treat hypertension.

Dr. Lipicky mentioned that a combination of HCTZ (a drug that may have a weak mutagenic effect) and CS-866 might have an additive mutagenic effect. He suggested that the firm do mutagenicity studies with the combination. The firm asked what ratios of the individual components of the combination should be used. Dr. Lipicky said he could not quantify the ratios to use but urged the firm to use a number of different ratios to see what effect, if any, they have on the rate of chromosomal abnormalities. Dr. Fenichel mentioned that the firm might want to do mutagenicity testing with competitors' products and their product in a verifiably blinded trial. They could then possibly show that other sartans produce similar in-vitro mutagenic effects.

The firm asked how the Division weighed in-vitro versus in-vivo results. Dr. Resnick said that the Division weighs the in-vitro results more heavily because they are usually the more sensitive tests.

Conclusion

Dr. Lipicky said that the proposed trials were acceptable, although they could be modified to provide more dosing information. He said that because of the in-vitro mutagenic effects of CS-866 and HCTZ, the firm would have to conduct tests with the combination CS-866/HCTZ to determine whether the mutagenic action of the two drugs are additive. He invited the firm to meet with the Division on how to proceed with mutagenicity studies for the combination product.

Dr. Resnick said it would be helpful if the firm would send in the results of the 2 year rat and transgenic mouse studies ahead of the planned NDA submission. He also said the Division would contact the firm as to whether a developmental toxicity study in pregnant rabbits is needed for the combination product.

Minutes Preparation: ES
Edward Fromm

Concurrence: ES
Raymond Lipicky, M.D.

dr/2-17-00/3-15-00

Rd: JHung-3/10/00
EFadiran-3/13/00
GJagadeesh-3/14/00
CResnick-3/14/00
STargum-3/14/00
RFenichel-3/15/00

cc: IND
HFD-110
HFD-110/Blount
HFD-110/EFromm/SMatthews

19. Financial Information

The Certification: Financial Interests and Arrangements of Clinical Investigators (Form FDA 3454) is provided on the following pages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

✓ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
See attached list	

✓ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

✓ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Thomas Robinson, M.D.	Vice President, Clinical Development
FIRM/ORGANIZATION	
✓ Sankyo Pharma Development	
SIGNATURE	**DATE**
Thomas D. Robinson	June 28, 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

18 Page(s) Withheld

19 Draft Labeling Page(s) Withheld

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: August 12, 2002	**DUE DATE:** October 12, 2002	**ODS CONSULT #:** 02-0169

TO: Douglas Throckmorton, MD
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Edward Fromm
Project Manager
HFD-110

PRODUCT NAME:	**NDA SPONSOR:**
Benicar HCT (Olmesartan Medoxomil and Hydrochlorothiazide Tablets) 20 mg/12.5 mg, 40 mg/12.5 mg, and 40 mg/25 mg **NDA: 21-532**	**Sankyo Pharma Inc.**

SAFETY EVALUATOR: Kevin Dermanoski, RPh

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name Benicar HCT to determine the potential for confusion with approved proprietary and established names as well as pending names. In addition, the package insert labeling and the *Physician Sample* carton labeling were reviewed for possible interventions to minimize medication errors. The container labels and carton labeling were not submitted and thus were not reviewed.

DMETS RECOMMENDATION:

1. DMETS has no objections to the use of the proprietary name, Benicar HCT. However, upon the launch of Benicar HCT, DMETS recommends that the sponsor educate healthcare professionals and patients on the similarities and differences between Benicar and Benicar HCT and the appropriate use of this combination product.
2. DMETS recommends implementing the labeling revisions outlined in Section III of this review to minimize medication errors.
3. DMETS requests the submission of a complete set of container labels and carton labeling for review when they are available.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-9664

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 10, 2002

NDA# 21-532

NAME OF DRUG: Benicar HCT
(Olmesartan Medoxomil and Hydrochlorothiazide Tablets)
20 mg/12.5 mg
40 mg/12.5 mg
40 mg/25 mg

NDA HOLDER: Sankyo Pharma Inc.

I. INTRODUCTION:

Sankyo Pharma Inc. currently markets Benicar (olmesartan medoxomil) that was approved on April 25, 2002 under NDA 21-286. Benicar is supplied as 5 mg, 20 mg, and 40 mg oral tablets. The sponsor has submitted NDA 21-532 for the approval of a combination drug product containing olmesartan medoxomil and hydrochlorothiazide under the proposed proprietary name Benicar HCT.

In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Benicar HCT" to determine the potential for confusion with approved proprietary and established names as well as pending names. In addition, the package insert labeling and the *Physician Sample* carton labeling were reviewed for possible interventions to minimize medication errors. The container labels and carton labeling were not submitted and thus were not reviewed.

PRODUCT INFORMATION

Benicar HCT combines an angiotensin II receptor antagonist, olmesartan medoxomil, and a diuretic, hydrochlorothiazide. Benicar HCT is indicated for the treatment of hypertension, however the fixed dose combination is not indicated for initial therapy.

Benicar HCT will be available in three combination strengths, namely, 20 mg/12.5 mg, 40 mg/12.5 mg, and 40 mg/25 mg. Each combination strength will be available in bottles of 30, 90, —, and 1000 tablets. In addition, Benicar HCT will be available in unit-dose packaging as 10 blister cards of 10 tablets.

II. RISK ASSESSMENT:

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name "Benicar" has been used in the U.S. marketplace since April 2002. A search was conducted of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to Benicar HCT to a degree where potential confusion between drug names could occur under the usual clinical practice settings. Searches of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[4] and the Saegis[5] Pharma-In-Use database were also conducted. Since the proprietary name Benicar is an approved drug product, the standard DMETS prescription analysis studies were not conducted.

The FDA Adverse Event Reporting System (AERS) was searched for any post-marketing safety reports of medication errors associated with the name Benicar. AERS was also searched for post-marketing safety reports of medication errors associated with the modifier 'HCT.'

A. REFERENCE SEARCH

The search of the reference texts and databases did not identify any sound-alike or look-alike names of concern.

DDMAC did not have concerns about the name Benicar HCT with regard to promotional claims.

B. AERS DATABASE SEARCHES

The Adverse Event Reporting System (AERS) was searched for all post-marketing safety reports of medication errors associated with Benicar. The MEDDRA Preferred Term (PT) "Medication Error" and the terms "Benicar," "Olmesartan," "Beni%," and "Olmes%" were used as search criteria. The search did not identify any cases relating to name confusion with Benicar.

The electronic Orange Book was searched for all approved products that contain the modifier 'HCT.' This search yielded the following products: Lotensin HCT, Atacand HCT, Teveten HCT, Monopril HCT, Lopressor HCT, Micardis HCT, and Diovan HCT. In all cases the 'HCT' represents hydrochlorothiazide. The AERS database was searched using the Preferred Term "Medication Error" and the proprietary and established name of

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

[4] WWW location http://www.uspto.gov/tmdb/index.html.

[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

the aforementioned products. Ninety reports were identified. Of these reports, two cases involved confusion with the modifier "HCT."

C. SAFETY EVALUATOR RISK ASSESSMENT

A search of the AERS database did not identify any medication error reports involving name confusion with Benicar. Therefore, there is no evidence at this time to conclude that the root name, Benicar, has significant potential for name confusion.

The search of the Adverse Events Reporting System identified two cases associated with confusion with the modifier 'HCT.'

1. In the first case, there was confusion between Lotensin HCT 10 mg/12.5 mg and Lotensin HCT 20 mg/12.5 mg. A prescription was filled with the wrong strength. There are no other details provided in the report. (AERS ISR# 36764000-4)

2. In the second case, there was confusion between Lopressor and Lopressor HCT. The prescription was written for Lopressor 100 mg/25 mg #30. The technician misinterpreted the prescription and typed a label for Lopressor 100 mg #30. "The technician who was refilling the prescription caught the error and reported it to the pharmacist. The pharmacist then had the script canceled and told the patient we didn't have the medication that the Dr originally wrote for." A note was "placed in the patient's chart and a caution to everyone to pay close attention for the prescriptions." There are no other details in the report. (AERS ISR# 3693139-X, USP# 53850).

The overlapping strengths between Benicar and Benicar HCT (See Table 1 below) may increase the potential for name confusion. DMETS is concerned with the potential consequences of medication errors if a prescription for Benicar is filled with Benicar HCT and vice versa. If patients receive Benicar in place of Benicar HCT, the desired reduction of blood pressure may not occur. If patients receive Benicar HCT in place of Benicar, patients may experience the risk of hypotension and hypokalemia. Potential errors may be reduced by education at the launch and by differentiating the labels and labeling for Benicar and Benicar HCT.

Table 1

Proprietary Name	Olmesartan	Hydrochlorothiazide
Benicar 5 mg	5 mg	
Benicar 20 mg	20 mg	
Benicar HCT 20 mg/12.5 mg	20 mg	12.5 mg
Benicar HCT [redacted] mg	40 mg	
Benicar [redacted] mg/12.5 mg	40 mg	12.5 mg
Benicar HCT [redacted] mg/25 mg	40 mg	25 mg

Postmarketing experience reveals that a suffix or modifier will not guarantee differentiation between products. Other characteristics such as strength, directions for use, labels, labeling, and product appearances are all very important features that can aid in the prevention of errors. As noted above, Benicar and Benicar HCT will have similar strengths and dosing recommendations. This reinforces the need to educate healthcare providers upon the launch

of the new combination product in order to prevent errors. Not only will healthcare providers need to be informed that a new combination product will be available in the U.S. marketplace, but they must also be warned that the new combination product and the single ingredient product have common characteristics (e.g., strength and dosing intervals). The education campaign should also provide precise information on the process of switching patients from one formulation to the other to prevent confusion and potential medication errors.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

The package insert labeling and the *Physician Sample* carton labeling were reviewed for possible interventions to minimize medication errors. The container labels and trade carton labeling were not submitted and thus were not reviewed.

A. GENERAL COMMENTS

1. To decrease the potential for confusion between Benicar and Benicar HCT the labels and labeling should be differentiated using contrasting design, color, boxing, or some other means.

2. The unit of measure should be listed with the amount of each ingredient in the product. For example, " " should be revised to read "20 mg/12.5 mg."

3. The strength of the product should be located in conjunction with the established name. Revise accordingly.

4. The Poison Prevention Act requires that unit-of-use containers have a child-resistant closure. We note you intend to market bottles of 30 and 90 tablets. These packaging configurations have the potential to be used as unit-of-use products. Please ensure the container has a child resistant closure.

B. PACKAGE INSERT

See General Comments A2 and A3 and revise accordingly.

IV. RECOMMENDATIONS:

A. DMETS has no objections to the use of the proprietary name, Benicar HCT. However, upon the launch of Benicar HCT, DMETS recommends that the sponsor educate healthcare professionals and patients on the similarities and differences between Benicar and Benicar HCT and the appropriate use of this combination product.

B. DMETS recommends implementing the labeling revisions outlined in Section III of this review to minimize medication errors.

C. DMETS requests the submission of a complete set of container labels and carton labeling for review when they are available.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Kevin Dermanoski, RPh Date
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise Toyer, Pharm D Date
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kevin Dermanoski
10/24/02 11:20:54 AM
PHARMACIST

Denise Toyer
10/25/02 08:15:05 AM
PHARMACIST

Carol Holquist
10/25/02 08:19:46 AM
PHARMACIST

Jerry Phillips
10/25/02 11:45:17 AM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-532

Sankyo Pharma Inc.
Attention: Mr. Albert S. Yehaskel
399 Thornall Street, 11th Floor
Edison, NJ 08837

Dear Mr. Yehaskel:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Benicar HCT (olmesartan medoxomil and hydrochlorothiazide) Tablets
Review Priority Classification:	Standard (S)
Date of Application:	August 5, 2002
Date of Receipt:	August 5, 2002

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 4, 2002 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 4, 2003.

All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

Mr. Edward Fromm
Regulatory Project Manager
(301) 594-5332

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Acting Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Zelda McDonald
8/12/02 09:34:09 AM